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Tandem ring-closing metathesis reaction with a ruthenium catalyst containing a N-heterocyclic ligand

Tae-Lim Choi and Robert H. Grubbs*

Arnold and Mabel Beckman Laboratories of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, USA. E-mail: rhg@its.caltech.edu

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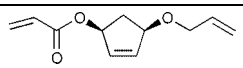
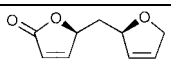
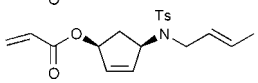
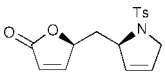
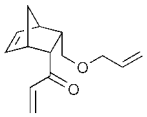
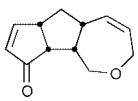
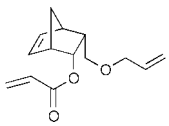
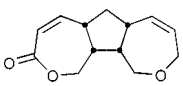
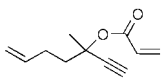
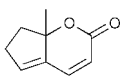
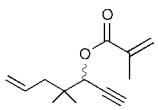
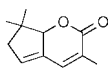
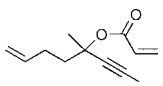
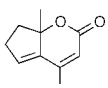
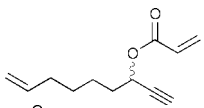
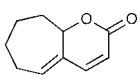
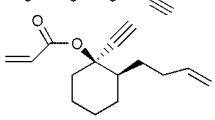
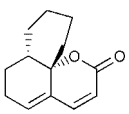
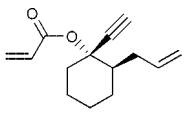
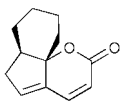
The highly active catalyst 2 was used in tandem RCM to make molecules with various ring systems containing α,β-unsaturated carbonyl compounds.

Tandem cyclization reactions build up molecular complexity rapidly from relatively simple starting substrates.[1] Complicated molecules were synthesized in a single step by carbanion,[2] carbocation,[3] free radical,[4] and Pd coupling reaction[5] whose novelty and efficiency were demonstrated by total syntheses of many natural products. Olefin metathesis has become a useful reaction in organic synthesis,[6] and our group recently demonstrated the viability of tandem ring closing metathesis reactions using catalyst **1**.[7] Unfortunately, catalyst **1** could not incorporate more synthetically valuable functionalized olefins such as α,β-unsaturated carbonyl compounds. However, with the development of the more active catalyst **2**,[8] containing a N-heterocyclic ligand, functionalized olefins could participate in RCM and cross metathesis reactions.[9] Herein, we report tandem RCM reactions by using catalyst **2**, to make synthetically useful α,β-unsaturated lactones and enones.

Various substrates containing different olefin arrays were examined for the tandem cyclization and were found to give moderate to excellent yields (Table 1). Entries 1 through 4 demonstrate the viability of tandem ring-opening/ring-closing

Table 1 Tandem RCM to install functionalized olefins[a]

Entry	Substrate	Concentration	Product	Yield
1		0.05 M		**3**: 81%
2		0.05 M		**4**: 89%
3		0.005 M		**5**: 45%
4		0.005 M		**6**: 47%
5		0.03 M		**7**: 95%
6		0.03 M		**8**: 86%
7		0.03 M		**9**: 72%
8		0.015 M		**10**: 68%
9		0.03 M		**11**: 100%
10		0.06 M		**12**: 74%

[a] 5 mol% catalyst **2** at 40 °C in CH_2Cl_2 for 6–12 h.

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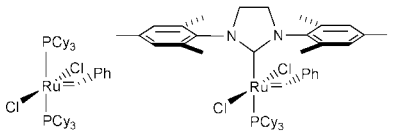

1 2

metathesis. In the case of entries 1 and 2, catalyst **2** reacts with more reactive terminal olefin and the resulting alkylidene opens the 5-membered ring. The sequence of tandem events is completed by ring closing onto the α,β-unsaturated carbonyl olefin (Scheme 1). Fused tricyclic compounds were also synthesized from the highly strained norbonene moiety, but the yields were lower due to competing polymerization (entries 3 and 4).

Another variant of tandem RCM is demonstrated by enyne tandem ring closing metathesis to form fused bicyclic ring systems (entries 5 to 10). In these cases, catalyst **2** also reacts with the terminal olefins preferentially and undergoes rapid intermolecular enyne metathesis to form the first ring, then reacts with the α,β-unsaturated carbonyl olefin to close the final ring (Scheme 2). The fact that 7-membered lactone **A** is never observed, implies that during the first RCM event, the newly formed alkylidene **B** exclusively reacts with acetylenes over acrylates. The more challenging trisubstituted α,β-unsaturated carbonyl olefins were also successfully cyclized (entries 6 and 7). However, an attempt to make a tetrasubstituted α,β-unsaturated carbonyl olefin afforded less than 10% yield of the bicycle with the remainder being monocyclized product. This suggests that disubstituted carbene is formed just as in entry 7, but preferentially reacts with the terminal olefins of the starting molecule over the sterically and electronically demanding α-disubstitued α,β-unsaturated carbonyl olefin. 7,6-Fused bicyclic compounds are available in moderate yield by this method, (entry 8). Lastly, tandem RCM to make 6,5,6- and 6,6,6-fused tricyclic compounds are shown in entries 9 and 10 which demonstrates that this method has potential applications in the synthesis of complex natural products.

The highly active catalyst **2** was used in tandem RCM to make molecules with various ring system. The ability to incorporate α,β-unsaturated carbonyl olefins makes the tandem RCM synthetically more valuable since further manipulations are possible.

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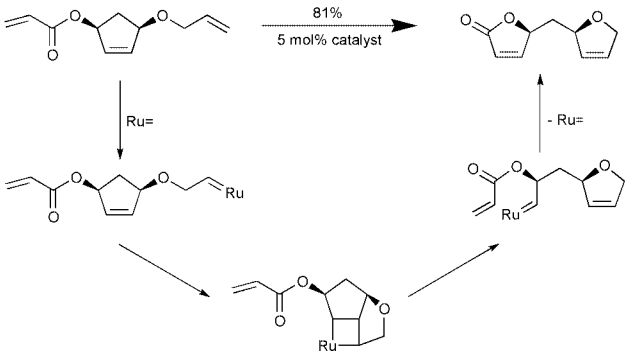
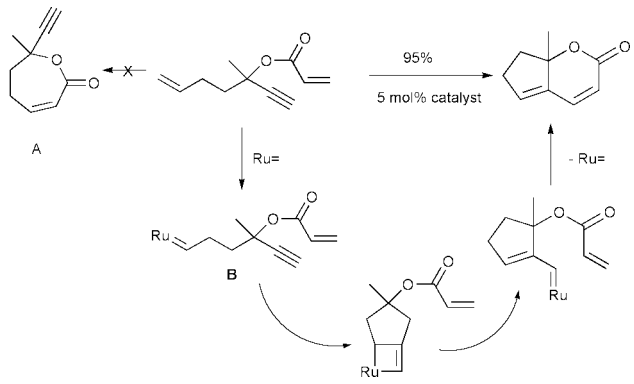


Scheme 1 Ring-opening/Ring-closing tandem RCM.



Scheme 2 Eyn-tandem RCM.

Notes and references

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